

# COMMENTARY

## Pulmonary hypertension and the search for the selective pulmonary vasodilator

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Pulmonary hypertension refers to a group of diseases characterised by high pressures in the pulmonary artery and pulmonary vascular resistance. The disease can be either secondary to an identifiable underlying pulmonary, cardiac, or systemic disease or primary with no identifiable underlying cause. Primary pulmonary hypertension is a progressive disease that mostly affects young individuals, is more common in women, and has a mean survival between 2 and 3 years from the time of diagnosis.<sup>1-3</sup> The management of pulmonary hypertension remains limited by poor understanding of its pathogenesis and by the lack of a selective pulmonary vasodilator. Discoveries in the nitric oxide (NO) field, however, are providing insights on both fronts.

The discovery that endothelial-derived relaxing factor was nitric oxide<sup>4,5</sup> brought this highly reactive free-radical gas out of obscurity as an environmental pollutant and put it centre-stage scientifically, and led to an explosion in knowledge about NO and its role in human physiology and disease.<sup>6,7</sup> NO is endogenously synthesised by nitric oxide synthases (NOSs) which convert L-arginine to L-citrulline and NO in the presence of oxygen and several cofactors.<sup>6,8</sup> Three NOSs (types I, II, and III) have been identified<sup>6</sup> and are widely expressed in various tissues, including the lungs.<sup>9</sup> NO can also be detected in exhaled breath.<sup>10,11</sup> Once produced, NO is freely diffusible and enters pulmonary smooth-muscle cells to activate soluble guanylate cyclase and produce guanosine 3',5'-cyclic monophosphate (cGMP).<sup>8</sup> The unique anatomy of the lung with the close proximity of the airways to the blood vessels allows NO that is produced in high levels in the upper<sup>12</sup> and lower airways by NOSII<sup>11</sup> to affect pulmonary vascular tone, in concert with the low NO levels that are produced by NOSIII in the vascular endothelium. As soon as the job of this potent vasodilator is done in the lung, it is bound to haemoglobin and thus has virtually no effects on systemic haemodynamics—ie, NO is a truly selective pulmonary vasodilator.

Interestingly, patients with primary pulmonary hypertension have low levels of NO in their exhaled breath.<sup>13</sup> Although far more complex than the simple lack of a vasodilator, replacement of NO seems to work well in treating the problem.<sup>14</sup> Exogenous administration of NO gas by inhalation is probably the most effective and specific therapy for primary pulmonary hypertension.<sup>1,3,14</sup> Cost and unresolved technical difficulties in the delivery of inhaled NO, however, have prevented its widespread

use.<sup>14</sup> In the meantime, epoprostenol analogues have revolutionised therapy in patients with primary pulmonary hypertension. Such analogues seem to exert their beneficial effect at least in part through NO,<sup>15</sup> but they are also cumbersome to administer and require a constant infusion with its related complications. Thus the search for an orally administered selective pulmonary vasodilator has been on for a while. Agents that can release NO or affect endogenous NO production are the logical targets.

In this issue of *The Lancet*, Hossein Ghofrani and colleagues report the use of sildenafil, a phosphodiesterase type 5 inhibitor, in patients with pulmonary hypertension secondary to lung fibrosis. 16 patients with severe lung fibrosis of different causes were diagnosed with secondary pulmonary hypertension by right-heart catheterisation. All patients were initially given inhaled NO and were then randomised to receive either intravenous prostacyclin (the current standard of care for treatment of primary pulmonary hypertension) or oral sildenafil. Haemodynamics and ventilation-perfusion (V/Q) matching were recorded before and after the administration of each agent. Whilst all three agents reduced mean pulmonary artery pressure, the ratio of pulmonary to systemic vascular resistance decreased only after NO and sildenafil. Prostacyclin worsened the V/Q mismatch and decreased arterial oxygenation while NO and sildenafil improved overall V/Q matching. In the sildenafil group arterial oxygenation was also improved. The investigators speculate that sildenafil works by amplifying local vasoregulatory mechanisms still maintained in the diseased lung. By inhibiting phosphodiesterase type 5, sildenafil stabilises cGMP (the second messenger of NO), allowing a more sustained effect of endogenous NO. This study clearly shows that sildenafil is a more selective pulmonary vasodilator than other currently available agents, such as calcium-channel blockers and prostacyclin. Sildenafil falls short, however, of being a truly selective pulmonary vasodilator. A truly selective pulmonary vasodilator (like inhaled NO) should not affect systemic blood pressure, which was not the case with sildenafil. Systemic blood pressure dropped in patients receiving sildenafil and prostacyclin but not in patients receiving inhaled NO.

Thus the study by Ghofrani and colleagues adds to growing evidence for the use of sildenafil as a pulmonary vasodilator in patients with primary and secondary pulmonary hypertension.<sup>16-18</sup> To date, this is the best

available orally administered selective pulmonary vasodilator, and the search goes on.

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## Breast is best for preventing asthma and allergies—or is it?

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One of the major changes in thinking over the past decade has been the growing realisation of the importance of early life events in the development of many childhood and adult diseases, especially asthma and allergies. Genetic susceptibility certainly has a substantial role in determining who develops asthma, but is alone not sufficient. Environmental factors are clearly important and that they interact with genetic susceptibility is well accepted. However, this gene-environment model is not sufficient to describe the

initiation phase of a complex disease such as asthma; the developmental stage at which this interaction occurs is critical to outcome.<sup>1</sup> Both the physiological and immunological seeds for asthma that persist into adolescence and adulthood are determined by early life events. In particular the programming of aberrant pattern(s) of immunological memory specific for inhalant allergens, and inflammatory damage to lung and airway tissue occurring during the critical phase of growth in early childhood, have serious long-term consequences for the way lungs and airways function. One of the important exposures in early infancy is breastfeeding. Although it would take a brave paediatrician to argue against the benefits of breastfeeding, there is no consensus about whether breastfeeding protects against the development of asthma and allergies.

Exposing infants to food allergens, especially cows' milk protein in early life, has been claimed to increase the likelihood of developing atopy and asthma.<sup>2</sup> These views led to a number of studies, typified by those on the Isle of Wight pioneered by the late David Hide,<sup>3</sup> which failed to demonstrate a convincing reduction in the prevalence of allergic sensitisation and asthma from dietary restrictions of infants, nursing mothers, or pregnant women. Similarly, the effects of breastfeeding on the risk of developing asthma and allergies are conflicting. Recent studies from birth cohorts in Perth<sup>3</sup> and Tucson<sup>4</sup> highlight this conflict. Oddy and colleagues,<sup>3</sup> studying a community-based birth cohort of about 3000 children, reported that introduction of milk other than breastmilk before the age of 4 months increased the risk of wheezing outcomes. The non-breastfed infants had a 25% increased risk of doctor-diagnosed asthma at age 6 years (odds ratio 1.25, 95% CI 1.02–1.52), and a 30% increased risk of having a positive skin-prick test to at least one aeroallergen (1.30, 1.04–1.61). This cohort was recruited antenatally and not selected on any asthma, atopy, or respiratory variables.<sup>5</sup> Breastfeeding had previously been reported to decrease the incidence of acute respiratory infections in early life, in particular those due to respiratory syncytial virus.<sup>6</sup> In the Perth study at least half the protection against wheezing by breastfeeding could be attributed to fewer lower respiratory illnesses associated with wheezing in the first year of life. Such wheezing was a major risk factor for wheezing outcomes at age 6 in this population. But this factor did not explain all of the effect.<sup>7</sup> Wright and colleagues,<sup>4</sup> reporting from the Tucson cohort study (1246 people), showed that the relation between breastfeeding, asthma, and wheeze at age 13 years differed with the presence of maternal asthma and atopy in the child: atopic children with asthmatic mothers were more likely to have asthma if they had been exclusively breastfed in early life (8.7, 3.4–22.2), even after adjusting for confounders. This effect was seen whether the duration of exclusive breastfeeding was under or over 4 months, but was not seen in children from non-asthmatic mothers.<sup>4</sup> There was no effect of paternal asthma on this relation.<sup>4</sup> Like the Perth study,<sup>3</sup> Wright and colleagues<sup>4</sup> also showed that breastfeeding was associated with a lower prevalence of wheeze in the first 2 years of life (0.45, 0.2–0.9).

In today's *Lancet*, Malcolm Sears and colleagues report the long-term outcome of a longitudinal study of children born in Dunedin, New Zealand, in the early 1970s, and show an increased risk of asthma in children who were breastfed. Initially 1661 children were included in an intensive neonatal study<sup>8</sup> and 1037 (91%) of 1139 eligible children at the age of 3 years were enrolled for